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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/111,123	07/06/1998	HABIB ZAGHOUANI	ALLIA143	5474

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/111,123	ZAGHOUANI, HABIB	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-27* is/are pending in the application.

4a) Of the above claim(s) *8-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7, and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response received March 21, 2005 is acknowledged.

Claims 1 and 3-27 are pending.

Claims 1 and 21 have been amended.

Claims 8-20 stand withdrawn from consideration.

Claims 1, 3-7 and 21-27 are under examination in this office action

Priority

2. Applicant is thanked for updating the first line of the specification to indicate that application 08/779,767 has issued as US Patent 6,737,057.

Specification

3. The disclosure is objected to because of the following informalities:

The autoimmune disease systemic lupus erythematosus (lupus) is not customarily referred to as "lupis" as is found on pages 16 and 31 of the instant specification.

A non-initialed handwritten correction appears on line 13 of page 31

Appropriate corrections are required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

4. Claims 4 and 23 stand objected to because of the following informalities: The autoimmune disease lupus is misspelled. This objection was made in the office action mailed August 10, 2004, and has not been addressed by Applicant. Appropriate correction is still required.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3-7 and 21-27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the reasons of record set forth in paragraph 5 of the office action mailed August 10, 2004.

Applicant's arguments filed March 21, 2005 have been fully considered but they are not persuasive. Applicant has argued that the structure of the claimed fusion protein

is predictable (in that it is predominantly an antibody, the structure of which has been know for some time) and that T cell receptor antagonists have been identified in the prior art for many autoimmune diseases, and therefore they do not need to be disclosed in the instant specification since they would be known to skilled artisans. Applicant also has amended base claims 1 and 21 to limit the autoimmune disorder of which symptoms are being alleviated to multiple sclerosis, rheumatoid arthritis, and insulin dependent diabetes.

The examiner agrees with applicant that the generalized structure of the fusion protein is well known. However, the identity of the antagonist to be used in the fusion protein is the portion of the fusion protein that will differ in structure. The examiner agrees with applicant that T cell antagonists for multiple sclerosis, rheumatoid arthritis, and type I insulin dependent diabetes mellitus were known to skilled artisans at the time the invention was filed. However, the claims as currently recited do not require that the T cell antagonist is specific for autoreactive T cells associated with said autoimmune disorders, and in dependent claims 4 and 23 the T cell antagonists are associated with autoimmune diseases different from those disorders recited in the preamble. The structure and identity of peptide antagonists other than those associated with multiple sclerosis, rheumatoid arthritis, and type I insulin dependent diabetes mellitus are not found in the disclosure, and evidence indicating that said antagonists were known to skilled artisans at the time the invention was filed has not been presented by Applicant. As such the rejection has been maintained.

It is noted that the instant claims recite insulin dependent diabetes, and some type II diabetic patients are insulin dependent. Type II diabetes is not considered an autoimmune disease and as such this disease has been considered by the examiner not to be part of the disorders that can be treated using Applicant's fusion protein. If this interpretation is not correct, Applicant is invited to show evidence that antagonists of insulin dependent type II diabetes were known in the art at the time the invention was filed.

3. The rejection of claims 1, 3-7 and 21-27 under 35 U.S.C. 112, first paragraph, scope of enablement, of record as paragraph 6 of the office action mailed august 10, 2004 has been withdrawn due to Applicant's claim amendment and the arguments set forth in the response received March 21, 2005.

The response indicates that "[t]he phrase 'preventing activation of autoreactive T cells' presumes from the time period forward after administration of the claimed composition." Support for such an interpretation of "prevents" appears to be most clearly found on page 34, lines 16-25, of the instant specification. This passage indicates that the antagonist is thought to prevent activation of the autoreactive T cells by a competitive inhibition mechanism. Note that this is not the mechanism by which Applicant currently believes the invention to work, as evidenced by Applicant's arguments found on page 11 of the reply filed March 21, 2005, wherein it is stated that "[t]he interaction between antagonist/MHC complexes and the autoreactive T cells reduces cytokine production, thereby inactivating autoreactive T cells."

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1, 3-4, and 21-24 stand rejected under 35 U.S.C. 102(e) as being anticipated by Deo et al., U.S. Patent Number 5,837,243 (see entire document) for the reasons of record set forth in paragraph 8 of the office action mailed August 10, 2005.

Applicant's arguments filed March 21, 2005 have been fully considered but they are not persuasive. Applicant argues that the structure of the molecule taught by Deo et al. differs from the structure of the molecule claimed in the instant application. The examiner respectfully disagrees. The examiner agrees with applicant that the structure of the molecules taught by Deo et al. differ in structure from the molecules disclosed in the instant specification. However, the requisite structure of a molecule sufficient to meet the limitations of the instant claims requires 1) an immunoglobulin molecule or a portion thereof that contains an immunoglobulin constant region, 2) a T cell receptor antagonist, and 3) the covalent joining of parts 1 and 2 into a fusion protein. Deo et al. teaches such a molecule (see entire document, particularly Example 7). The claimed

fusion protein must also be endocytosed by antigen presenting cells and be presented with MHC class II. Deo et al. teaches such a molecule (see particularly column 32, lines 6-8). The claimed fusion protein prevents the activation of autoreactive T cells specific for the T cell receptor antagonist. The fusion protein of Deo et al. specifically inhibits the proliferation of antigen specific T cells, and proliferation is one common way to measure T cell activation (see particularly lines 52-67 of column 31 and lines 1-11 of column 32). Deo et al. also teach that their fusion proteins are to be used in the treatment of autoimmune disorders including rheumatoid arthritis, multiple sclerosis, and lupus (column 11, line 19, and column 33, first full paragraph, especially lines 16-17). Therefore, the structure of the fusion protein taught by Deo et al. meets all of the claimed limitations. Applicant discusses at length how the fusion proteins of Deo et al. work by a different mechanism that the fusion proteins taught in the instant specification. Such a discussion is irrelevant since it argues limitations that are not currently recited in the claims, and the rejection of record is maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 5, 21 and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Deo et al., U.S. Patent Number 5,837,243 in view of Karin et al. (J. Exp. Med, 1994, 180: 2227-2237) for the reasons of record set forth in paragraph 10 of the office action mailed August 10, 2005.

Applicant's arguments filed March 21, 2005 have been fully considered but they are not persuasive. Applicant argues that since the fusion proteins of Deo et al. work differently from the fusion proteins taught in the instant application, combining the teachings of Deo et al. with those of Karin et al. would not generate a fusion protein with the requisite claimed properties. As discussed above, Applicant is arguing limitations not recited in the claims with regard to the teachings of Deo et al., and as such combining the teachings of Deo et al. and Karin et al. does yield a fusion protein containing the requisite claimed properties.

8. Claims 1, 6, 21 and 26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Deo et al., U.S. Patent Number 5,837,243 in view of Kuchroo et al., (J. Immunol. 1994, 153: 3326-3336) for the reasons of record set forth in paragraph 11 of the office action mailed August 10, 2004.

Applicant's arguments filed March 21, 2005 have been fully considered but they are not persuasive. Applicant argues that since the fusion proteins of Deo et al. work differently from the fusion proteins taught in the instant application, combining the teachings of Deo et al. with those of Kuchroo et al. would not generate a fusion protein

with the requisite claimed properties. As discussed above, Applicant is arguing limitations not recited in the claims with regard to the teachings of Deo et al. As such the examiner maintains that teachings of Deo et al. and Kuchroo et al. are properly combined and do yield a fusion protein that comprises the requisite claimed properties.

9. Claims 1, 7, 21 and 27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Deo et al., U.S. Patent Number 5,837,243 in view of Elliott et al. (J. Clin. Invest., 1996, 98: 1602-1612), Kuchroo et al., (J. Immunol. 1994, 153: 3326-3336) and Karin et al. (J. Exp. Med, 1994, 180: 2227-2237) for the reasons of record set forth in paragraph 12 of the office action mailed August 10, 2004.

Applicant's arguments filed March 21, 2005 have been fully considered but they are not persuasive. Applicant argues that there is no motivation to combine the references of record and that since the fusion proteins of Deo et al. work differently from the fusion proteins taught in the instant application, combining these teachings would not generate a fusion protein with the requisite claimed properties. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The appropriateness of Applicant's argument concerning limitations not recited in the claims with regard to the teachings of Deo et al. has been previously discussed. As such, the

examiner maintains that teachings of Deo et al., Elliott et al., Kuchroo et al. and Karin et al. are properly combined and do yield a fusion protein that comprises the requisite claimed properties.

Double Patenting

10. Claims 1, 3-4, 6, 21-24 and 26 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,737,057. Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons or record set forth in paragraph 14 of the office action mailed August 10, 2004.

Applicant has acknowledged this rejection in the reply received March 21, 2005 and has requested the right to revisit the issue after the instant claims are allowed. Applicant is reminded that the claims will never be allowed if there is an outstanding double patenting rejection of record that has not been removed due to amendments that change the scope to the claims such that they are no longer anticipated by the claims of U.S. Patent No. 6,737,057 or unless a terminal disclaimer is filed.

11. Applicant's amendment to the claims received March 21, 2005 has also necessitated a new ground of rejection.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 4, 21 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of the disorders identified in the base claims with antagonists specific for autoreactive T cells associated with said disorders, does not reasonably provide enablement for the treatment of said disorders with any antagonist, including antagonists that alleviate the symptoms of the autoimmune diseases recited in the dependent claims but not recited in the preamble of the base claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 1 recites a fusion protein that alleviates symptoms associated with multiple sclerosis, rheumatoid arthritis and insulin dependent diabetes, while claim 21 recites a fusion protein for treatment of multiple sclerosis and insulin dependent diabetes. The fusion protein in both claims contains a T cell receptor antagonist joined to at least part of an immunoglobulin constant region domain. Dependent claims 4 and 23 indicate that the antagonist portion of the fusion protein is capable of alleviating the symptoms of the autoimmune disorders multiple sclerosis, lupus, rheumatoid arthritis, scleroderma, insulin-dependent diabetes and ulcerative colitis.

Janeway et al. teach that different autoantigens are recognized in different autoimmune diseases (Immunobiology, 5th edition, chapter 13, downloaded from NCBI on 5/25/05, see entire document, particularly pages 1-3). As such, an antagonist that alleviates the symptoms associated with lupus would not be useful in treating multiple sclerosis since the autoreactive T cells present in multiple sclerosis are specific for autoantigens that are different from the autoantigens recognized by the autoreactive T cells of lupus patients, with the same relationship being found between the other recited disorders.

Applicant has not provided guidance or working examples of a T cell receptor antagonist that can interact with all autoreactive T cells present in all autoimmune diseases, and the teachings of Janeway et al. indicate that such an antagonist peptide does not exist given the diverse array of autoantigens recognized across the spectrum of autoimmune diseases and disorders. As such, the antagonists used in the claimed fusion protein must be specific for the disorder that is being treated as recited in the claim preamble in order to achieve the recited goal of alleviating disorder symptoms.

14. No claims are allowed.

15. Applicant's amendment necessitated the new ground of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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